Annals of Clinical and Analytical Medicine
Original Research

Effects of the genetic variants and serum levels of TIMP-1 and TIMP-2 on type 2 diabetes mellitus in the Turkish population

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Abstract

Aim: Genetic and environmental factors are very important in the formation of type 2 diabetes mellitus (T2DM). Tissue inhibitors of matrix metalloproteinases (TIMPs) play central roles in inhibition of the extent of extracellular matrix degradation. The aim of this study is to investigate serum levels and gene polymorphisms of TIMP-1 and TIMP-2, and their effects on T2DM in the Turkish population.

Material and Methods: One hundred seventeen patients with T2DM and 127 healthy controls were included in this study. TIMP-1 372 T>C, TIMP-2 303C>T, and TIMP-2 418 G>C polymorphisms were determined by PCR-RFLP method and serum TIMPs levels were measured by ELISA.

Results: The frequencies of the TT genotype and T allele of the TIMP-2 303 C>T polymorphism were significantly higher in the patient group than in the control group. The frequency of the C allele for TIMP-2 418 G>C polymorphism was significantly higher in the control group than in patients. TIMP-1 372 T>C polymorphism was not statistically significant between patients and controls. Additionally, TIMP-1 serum levels were statistically higher in T2DM patients than in controls.

Discussion: This study provides the first evidence that the TT genotype and T allele of the TIMP-2 303 C>T polymorphism significantly contribute to the risk of T2DM in the Turkish population. Also, carrying the C allele of the TIMP-2 418 G>C polymorphism had a protective effect against the development of T2DM. In addition, our results suggest that the C allele of the TIMP-1 372 T>C polymorphism may have protective effects against the development of T2DM.

Keywords

Type 2 Diabetes Mellitus (T2DM), Polymorphism, TIMP-1, TIMP-2, ELISA

DOI: 10.4328/ACAM.21788 Received: 2023-06-12 Accepted: 2023-11-27 Published Online: 2023-12-06 Printed: 2024-02-01 Ann Clin Anal Med 2024;15(2):94-98
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This study was approved by the Ethics Committee of the Faculty of Medicine, Istanbul University (Date: 2010-07-08, No: 233-41)

Introduction

Diabetes mellitus (DM) is one of the most common complex diseases in the world and is characterized by the ability to produce enough insulin. DM develops due to an increase in fasting glucose levels, accompanied by disturbances in lipid and protein metabolism [1]. Type 2 diabetes mellitus (T2DM) constitutes about 85–90% of diabetes cases and typically occurs in older age, but recently, it has also been seen in young adults and children [2]. The T2DM pathogenesis is controversial, its inheritance is polygenic, developing due to several abnormal genes or polymorphisms. For the presence of T2DM, a complex interaction between multiple genes and environmental factors is necessary [3].

Tissue inhibitors of metalloproteinases (TIMPs), first discovered in 1975, are natural inhibitors of the matrix metalloproteinase (MMP) and inhibit the proteolytic activity of MMPs. The TIMPs have four members (TIMP-1, 2, 3, and 4), and there are structural and biochemical differences between these genes [4]. An imbalance between TIMPs and MMPs causes pathological processes such as arthritis, aneurysm formation, plaque disruption, atherosclerosis and diabetic nephropathy [5]. It has been shown that plasma TIMP-1 and TIMP-2 levels are increased in type 1 and type 2 diabetic patients. TIMP-1 prevents the activation and enzyme activity of MMP-9, while TIMP-2 prevents the activation and enzymatic function of MMP-2. TIMP-1 and TIMP-2 are defectively synthesized, while MMP-9 and MMP-2 are excessively produced in chronic diabetic wounds of because TIMP-1 and TIMP-2 can bind non-covalently to MMP-9 and MMP-2 [6].

It has been established that TIMP-1 and TIMP-2 play various roles in the pathogenesis of diabetes [7]. However, until now, there have been no reports on the effects of TIMP-1 372 T>C, TIMP-2 303 C>T, and TIMP-2 418 G>C polymorphisms in the development of T2DM. Therefore, we investigated the association between TIMP-1 372 T>C, TIMP-2 303 C>T, and TIMP-2 418 G>C polymorphisms and T2DM in the Turkish population.

Material and Methods

Study group

One hundred seventeen T2DM patients and 127 healthy individuals were included in this study. The patients were followed up at the Department of Internal Medicine, Istanbul Training and Research Hospital, and Istanbul Medicana Hospital, Istanbul, Turkey. Healthy control subjects did not have any sign of a family history of diabetes mellitus. Serum and whole blood samples were taken from all individuals.

DNA isolation

The peripheral blood was taken from the volunteers (patients and healthy individuals) who agreed to participate in the study into tubes containing EDTA for DNA to be used in the study. The genomic DNA was obtained from these blood samples according to the salting-out method as described in our previous studies [8, 9]. All collected DNA samples were stored in Tris-EDTA buffer (Sigma-Aldrich, USA) at +4 °C until analysis.

SNP detection

The TIMP-1 372 T>C, TIMP-2 303 C>T, TIMP-2 418 G>C polymorphisms were analyzed from the isolated genomic DNA samples by PCR-RFLP as described in our previous studies [10, 11]. For detection of related polymorphisms, the reaction was performed in 25 µl volume containing genomic DNA, reaction buffer (Invitrogen, USA), dNTP (Invitrogen, USA), specific primer (Invitrogen, USA) for each, and Taq polymerase (Invitrogen, USA). The annealing temperature for TIMP-1 372 T>C, TIMP-2 303 C>T, and TIMP-2 418 G>C polymorphisms is 56 °C. The PCR products were restricted with convenient restriction enzymes (Invitrogen, USA), and then separated in a 3% agarose gel electrophoresis, visualized under ultraviolet light. All primers, restriction enzymes and genotyping used to identify these polymorphisms are presented in Table 1.

TIMPs assay

Fresh blood samples taken from all participants for ELISA analyzes were centrifuged at 3000 rpm for 5 minutes on the same day to ensure serum separation. Afterwards, serum samples were frozen and stored at -20 °C until ELISA analysis. Serum TIMP-1 and TIMP-2 levels were analyzed with ELISA using TIMP-1 and TIMP-2 human ELISA kits (Quantikine R&D System, USA).

Statistical analysis

Statistical analyzes were performed with the IBM SPSS 24.0 program (IBM, USA). The conformity of the data to the normality was determined with the Kolmogorov-Smirnov test. The normally distributed data were detected with the independent sample t-test. The data of the groups did not show normal distribution, the difference between the groups was evaluated with the Mann-Whitney test. Demographic parameters were stated as mean±standard deviation for data showing normal distribution, as median (min.-max.) for data showing abnormal distribution. Pearson's Chi-square test was evaluated to compare genotype and allele frequencies between groups. $p<0.05$ was considered significant.

Ethical Approval

The study was performed with the approval of the Ethics Committee of the Faculty of Medicine, Istanbul University, (Date: 2010-07-08, No: 233-41). Informed consent was obtained from each case included in the study.

Results

A total of 117 patients with T2DM and 127 controls were included in this study. The mean age of the patients with T2DM and healthy controls was 64.36 ± 8.82 and 59.78 ± 8.8 years,

Table 1. PCR-RFLP based assay of TIMP-1 372 T>C, TIMP-2 418 G>C and TIMP-2 303 C>T

SNPs	Primers	Restriction enzymes	Interpretations (bp)
TIMP-1 372 T>C	Forward Primer: 5'-GCACATCACTACCTGCAGTC-3' Reverse Primer: 5'-GAAACAAGCCCACGATTTAG-3'	BssSI	TT: 175 TC: 175 + 152 + 23 CC: 152 + 23
TIMP-2 418 G>C	Forward Primer: 5'- CGTCTCTTGTTGGCTGGTCA-3' Reverse Primer: 5'-CCTTCAGCTCGACTCTGGAG-3'	BsoBI	GG: 304 GC: 304 + 230 + 51 + 23 CC: 230 + 51 + 23
TIMP-2 303 C>T	Forward Primer: 5'- TAGGAACAGCCCCACTTCTG-3' Reverse Primer: 5'- CCTCCTCGGCAGTGTGTG-3'	TspRI	CC: 112 + 16 CT: 112 + 97 + 24 + 16 TT: 97 + 24 + 16

Table 2. Demographic details of T2DM patients and healthy control group

Groups		Age (Year)	BMI	LDL (mg/dl)	HDL (mg/dl)	VLDL (mg/dl)	Cholesterol (mg/dl)	Triglycerides	HbA1c	Creatinine
Patient	Mean±Std. deviation	63.91±9.11	29.26±3.94	117.97±37.25	40.21±19.18	38.13±20.88	192.18±41.85	185.48±20.73	8.32±6.48	1.41±2.96
	Minimum	39	19.53	31.8	9.2	9.6	100.2	46	4.50	0.4
	Maximum	87	42.11	232	197	250	338	309	8.7	3.Oca
	Median	65	28.91	119	38.6	36	194	169	7.35	0.9
Control	Mean±Std. deviation	63.83±13.59	27.94±4.90	112.99±35.45	43.79±13.16	34.90±16.73	191.15±39.40	176.34±85.28	4.6±1.33	1.13±1.04
	Minimum	19	19.53	26	21	7	114	37	3.41	0.15
	Maximum	84	42.11	211	92	107	326	536	5.56	8.19
	Median	61	28.91	113	42	33	187.6	165	4.43	0.81
p value		0.994	0.337	0.173	0.640	0.110	0.813	0.422	0.124	0.409

The Mann-Whitney U test (for age, BMI, HDL, VLDL, Triglycerides, HbA1c and Creatinine levels) and independent sample Test (for LDL and cholesterol levels) were used to evaluate the data. The values are reported as mean, standard deviation, minimum, maximum and median. p-values <0.05 were considered statistically significant.

Table 3. Genotype and allele frequencies of the TIMP-1 372 T>C, TIMP-2 418 G>C and TIMP-2 303 C>T polymorphisms among patients with T2DM patients and controls

SNPs	Genotypes and Alleles	Patients n (%)	Controls n (%)
TIMP-1 372 T>C	TT	52 (44.4)	70 (55.1)
	TC	54 (46.2)	46 (36.2)
	CC	11 (9.4)	11 (8.7)
	T	160 (68.4)	162 (68.4)
	C	74 (31.6)	92 (36.2)
TIMP-2 418 G>C	GG	84 (71.8)	82 (64.6)
	GC	19 (16.2)	26 (20.5)
	CC	14 (12)	19 (15)
	G	187 (79.9)	209 (61.5)
	C	47 (20.1)	131 (38.5)*
TIMP-2 303 C>T	CC	55 (47)	70 (55.6)
	CT	43 (28.2)	41 (32.5)
	TT	29 (24.8)**	15 (11.9)
	C	143 (44.1)	91 (56.2)
	T	181 (55.9)***	71 (43.8)

Pearson's Chi-square test was used to evaluate the data. The values were reported as number of patients (percentage of the total groups). *,**,***p-values<0.05 were considered statistically significant. *p=0.001, **p=0.033, ***p=0.012

respectively. There was no significant difference in age between the patient and control groups. LDL-Cholesterol (p:0.009) level was significantly higher in the patient group compared with the controls. It was also found that HDL-Cholesterol (P:0.037, 95% Cl:0.40-12.45) level was higher in the control group than in patients. The demographic parameters of the subjects and clinical characteristics of patients with T2DM are shown in Table 2.

The allele and genotype distribution of the study groups for TIMP-1 372 T>C, TIMP-2 303 C>T, and TIMP-2 418 G>C polymorphisms is presented in Table 3. Firstly, we evaluated the association of the TIMP-1 372 T>C polymorphism between type 2 diabetes patients and the control group. There was no statistical difference between the patients and the control group in terms of TIMP-1 372 T>C polymorphism.

T2DM patients and the control group were compared in terms of serum levels of TIMP-1 and TIMP-2. The TIMP-1 serum levels (p:0.001, 95% Cl:1.11-2.84) were statistically higher in type 2 diabetes patients (5.82 ± 2.37 ng/ml) than in the control group (3.84 ± 1.4 ng/ml). TIMP-2 serum level was 3.01 ± 0.97 ng/ml in the T2DM patient group and 2.92 ± 0.51 ng/ml in the control group, and there was no statistically significant difference between the two groups. In the patient group, serum levels of TIMP-1 and TIMP-2 were analyzed according to the genotype distributions in each of the three polymorphisms. There was no significant relationship between serum TIMP-1 and TIMP-2 levels and all three polymorphisms. In the control group, TIMP-1 levels were observed to be increased in individuals with CT genotype (p:0.015, 95% Cl:0.22 - 1.94).

Discussion

TIMPs are proteins that belong to a family of specific inhibitors and regulate the proteolytic activity of all MMPs. They also play a role in several biological activities such as cell differentiation, apoptosis, cell growth, invasion and angiogenesis [12]. The association between levels of TIMP-1 and TIMP-2 was previously evaluated in cardiovascular diseases [13, 14], sepsis [15], many cancers [7], obesity [16], and diabetes mellitus [17]. Lee et al. showed that plasma TIMP-1 concentration is significantly increased in patients with T2DM than in control subjects [18]. According to another study, the TIMP-1 and TIMP-2 levels were found higher in type 1 diabetic patients than in controls. Also, it is suggested that TIMP-1 plays a central role in the development of metabolic disorders in type 1 diabetes [19]. In diabetic nephropathy, circulating TIMP-1 and TIMP-2 were found to decrease in patients compared to either chronic renal failure or diabetes [20]. Moreover, Kanauchi et al. have suggested that TIMP-1 has a role in diabetic neuropathy and nephropathy [21]. In this study, TIMP-1 serum levels were statistically higher in T2DM patients than in the control group. No significant relationship was found between serum TIMP-1 and TIMP-2 levels and all three polymorphisms in the patients. In the control group, TIMP-1 levels were observed to be increased in individuals with the CT genotype.

The TIMP-1 372 T>C, TIMP-2 303 C>T, and TIMP-2 418 G>C polymorphisms have not been studied in diabetes mellitus; this study provides the first evidence. Lorente et al. have investigated the TIMP-1 serum levels and TIMP-1 372 T>C polymorphism in sepsis patients. They reported that septic patients carrying the T allele for the 372 T>C polymorphism of TIMP-1 had increased serum TIMP-1 levels and decreased survival rates [15]. The TIMP-1 372 C>T and TIMP-2 418 G>C polymorphisms were investigated in patients with endometrial cancer. Patients with

the TIMP-1 372 CC genotype were found to be at higher risk for endometrial cancer. However, no significant differences were found in the TIMP-2 418 G>C polymorphism between endometrial carcinoma individuals and healthy subjects [22]. Ikebuchi et al. have investigated the association between the TIMP-1 372 C>T and TIMP-2 418 G>C polymorphisms with the progression of chronic liver disease related to the hepatitis C virus. According to their results, it has been determined that the pathology of liver fibrosis was more advanced in individuals carrying the TIMP-2 418 GG genotype [23]. In a current study, the C allele frequency for the TIMP-2 418 G>C polymorphism was found significantly higher in abdominal aortic aneurysm patients than in healthy controls [24]. According to our results, there was no statistical difference in terms of the TIMP-1 372 T>C polymorphism between patients with T2DM and the healthy controls. C allele incidence of the TIMP-2 418 G>C polymorphism was not statistically significant between T2DM patients and the control group. When we compared the TIMP-2 303 C>T polymorphism between the study groups, the mutant TT genotype and T allele frequencies were found statistically higher in patients.

The small number of individuals included in the study is one of the factors limiting our results. It can be said that to exactly elucidate the role of TIMP-1 372 T>C, TIMP-2 303 C>T, and TIMP-2 418 G>C gene polymorphisms in T2DM, the number of individuals participating in the study should be increased and more studies should be conducted on this subject. However, even if only a small number of individuals were included in the study, the results may contribute to the understanding of the molecular mechanisms of TIMP genes in T2DM.

In conclusion, our findings provide new evidence for the association between TIMP-1 372 T>C, TIMP-2 303 C>T, and TIMP-2 418 G>C gene polymorphisms and the T2DM risk in the Turkish population. Our results suggest that the TT genotype and T allele of the TIMP-2 303 C>T polymorphism significantly contribute to the risk of T2DM in the Turkish population. Also, carrying the C allele for the TIMP-2 418 G>C polymorphism had a protective effect against the development of T2DM. In addition, our results suggest that the C allele for the TIMP-1 372 T>C polymorphism may have protective effects against the development of T2DM.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

Funding: *This study was supported by the Research Support Unit of Istanbul University, project no: 9865.*

Conflict of Interest

The authors declare that there is no conflict of interest.

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How to cite this article:

Faruk Celik, Umit Yilmaz, Nesibe Yilmaz, Kerem Ozyavuz, Cem Basaran, Osman Fazliogullari, Arzu Ergen, Umit Zeybek. *Effects of the genetic variants and serum levels of TIMP-1 and TIMP-2 on type 2 diabetes mellitus in the turkish population. Ann Clin Anal Med 2024;15(2):94-98*

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